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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,517	03/14/2001	William M. Sugden	960296.97982	4541

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	12

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/808,517	Applicant(s) SUGDEN ET AL.	
	Examiner Ulrike Winkler	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed February 7, 2002 (Paper No. 8) in response to the Office Action of October 2, 2002 is acknowledged and has been entered. Claims 15-19 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Specification

The office acknowledges the amendments to the specification correcting the typographical error.

Drawing

The office acknowledges the receipt of the drawings, which have been approved by the Draftsperson.

Claim Rejections - 35 USC § 112

The rejection of claims 15, 17 and 18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is withdrawn** in view of applicants amendments to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 15, 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mackey et al. (Journal of Virology, 1995) in view of Becker et al. (Israel Journal of Medicine, 1972) **is withdrawn.** Applicant's arguments with respect to claim 15, 16

and 19 have been considered but are moot in view of the new ground(s) of rejection [see below] necessitated by applicant's amendments to the claims.

Declaration

The declaration by William Sugden filed Paper No. 10 is insufficient to overcome the rejection of claim 15, 16 and 19 based upon Mackey et al. as set forth in the last Office action because: The declaration fails to provide any evidence that would indicate the nonobviousness of the prior rejection (or the new rejection below). The prior office action acknowledged that the Mackey et al. reference does not utilize whole cell extracts or whole cell assays, however the secondary reference utilized a whole cell inhibition assay comprising all the cellular components. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

New rejection in view of applicant's amendments to the claims:

Claims 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mackey et al. (Journal of Virology, 1995), Kirchmaier et al. (Journal of Virology 1997) and Becker et al. (Israel Journal of Medicine, 1972).

The instant invention is drawn to a method of screening candidate molecules that disrupt viral looping-linking factors in a cell. The cell is contacted with the inhibitor and the viral transcription or translation is assayed. The assay also requires that a viral looping/linking factor is present in the cell and that that the nucleic acid that is being looped/linked comprises at least two binding sites for the factor. The factor binding sites are interpreted to be on the nucleic acid

molecule in a plasmid. A plasmid by definition is a genetic element that is able to replicate independently of the host cell chromosome. The EBV viral DNA is interpreted as reading on a plasmid because the viral DNA is able to replicate independently of the host cell chromosome. Cells infected with EBV, Papilloma virus, Herpes Simplex virus or adenovirus all contain looping/linking proteins as well as nucleic acids (plasmids) that comprise at least two binding sites for the factor.

The experiments set out in the specification use Eletrophoretic Mobility Shift Assays (EMSA) in which small pieces of DNA that contain multiple protein binding sites are mixed with target protein [EBNA1 or recombinant proteins comprising EBNA linking domains in conjunction with a heterologous DNA binding domain]. The proteins comprise a DNA binding site that binds specific sequences of DNA and contains protein linker regions, which allow the protein to self-associate. In the absence of an inhibitor or candidate inhibitor compound the DNA-protein will from a high molecular weight matrix that will not enter into the gel. To form this matrix there are DNA-protein interactions and protein-protein interactions, both interactions are required for the formation of the high molecular weight matrix [termed linked-DNA in specification]. The DNA is labeled, therefore only the following three complexes can be seen on the gel: DNA, DNA-protein and linked DNA [which comprises DNA-protein and the additional protein-protein interaction]. This assay cannot visualize protein:protein interaction in the absence of DNA binding.

Mackey et al. teach that multiple regions with EBNA1 can link DNA's. This DNA linking is determined using EMSA. Mackey et al. established that high concentrations of EBNA1 would compete for the formation of linked complexes (see figure 1). The reference utilizes

DNA molecules that comprise at least two EBNA1 binding sites (page 6201, column 2, lines 3-18). The reference assays the ability of EBNA1 to link DNA and found as the concentration of EBNA binding sites increased on the DNA this in turn increased the linking of DNA. With the addition of excess EBNA1 the DNA linking is decreased because of competition with the bound complexes. The reference measures the ability of a compound to form large DNA lattices, thereby measuring the ability of EBNA1 to link DNA, utilizing EMSA. The reference teaches using an EBNA protein construct that has amino acids 330-641 of EBNA. As discussed in the declaration by W. Sugden in Paper No. 10, the reference does not utilize whole cell extracts which would have other cellular proteins present during the binding phase of the inhibitor with the nucleic acid binding site as required by the instant claims. The reference teaches an *in vitro* assay that measures the binding of the linker protein with the labeled DNA for the EMSA.

Kirchmaier et al. teaches an *in vivo* cell assay (see table 2) that tests the transcription inhibition [promoter activity assay] by various EBNA constructs including using an EBNA vector construct that encodes amino acids 330-641 of EBNA. Here the addition of EBNA derivatives acted as an inhibitor in the *in vivo* cell assay. The reference analyzed derivatives of EBNA-1 to activate transcription from a heterologous promoter (see results, page 1769, column1). The reference also tested whether the derivatives of EBNA-1 could inhibit transcription of EBNA-1 (page 1769, column 2). The reference utilizes the same amino acid construct that has been shown to link-DNA in an *in vitro* assay. The reference teaches using inhibitors in an *in vivo* cell assay.

Becker et al. disclose a cell-based assay to determine viral replication/inhibition here Burkitt lymphoma cells that comprise EBV were tested for their ability to inhibit EBV DNA

replication after treatment with distamycin. Burkitt lymphoma cells are latently infected with EBV and are positive for the presence of EBNA. Here the cells comprise DNA that contains more than one EBNA binding site as evidenced by the replication of the viral DNA. The cells are positive for EBNA indicating that they comprise a looping/linking factor. The reference teaches distamycin treated and untreated cells and compares the two cells for their EBV- DNA synthesis. The cells that were treated with distamycin did not replicate viral DNA indicating that distamycin is effective as an inhibitor for viral replication. The reference does not teach analyzing the ability of the looping/linking factor to be inhibited by an excess of the looping/linking factor.

In the development of pharmaceuticals there is a natural progression that begins with an observation between molecules, first an inhibitor and a target are assayed in a test tube. Assays in a test tube format allow the artisan to precisely study the interaction between known molecules. Once an inhibitor of a particular reaction is established the next natural step would be to see if the inhibitor will function the same way inside a cell, should the inhibitor not work inside a cell this would be the end of the investigation because it would be unnecessary to further study the effect of the inhibitor in an *in vivo* animal model. The declaration of W. Sugden (Paper No. 10) indicates that the instantly claimed assay differs from the assay of Mackey et al. in requiring whole cells. The question is whether the change in assay format *in vitro* to an *in vivo* setting would be an obvious step. It remains the position of the examiner that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to assay the EBNA linking competitors as taught by Mackey et al. as potential inhibitors for EBV infection utilizing the EBV cell inhibition assay as taught by Kirchmaier et al. or Becker et al.

There is a high expectation of success in utilizing the whole cell assay methods for determining the viral replication inhibition (Becker et al.). One having ordinary skill in the art would have been motivated to utilize the cell-based format to screen compounds for their ability to inhibit viral replication (Becker et al or Kirchmaier et al.) and determine at what point in the EBNA-1 cycle the inhibitor has an effect. Does the inhibitor disrupt DNA-protein or linked DNA complexes? The assay set out in Kirchmaier et al. cannot determine whether the effect is because of inhibitor disrupts DNA-protein or linked DNA complexes, the EMSA assay set out by Mackey et al. can determine where the inhibitor has an effect. There is great interest in developing inhibitors of EBV infection because immunosuppressed patients are latently infected with EBV. Therefore, the instant invention obvious over Mackey et al., Kirchmaier et al. and of Becker et al.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 7/28/03